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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/883,550	06/18/2001	William E. Marshall	P01936US5	1897

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EXAMINER	
ZEMAN, ROBERT A	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 12/22/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No.	Applicant(s)	
	09/883,550	MARSHALL, WILLIAM E.	
	Examiner	Art Unit	
	Robert A. Zeman	1645	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 10 October 2003 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☐ The period for reply expires _____months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☒ A Notice of Appeal was filed on *20 November 2003*. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☒ The proposed amendment(s) will not be entered because:

   (a) ☒ they raise new issues that would require further consideration and/or search (see NOTE below);

   (b) ☐ they raise the issue of new matter (see Note below);

   (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

   (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____.

3. ☒ Applicant's reply has overcome the following rejection(s): see attached.

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☒ The a)☒ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *see attached*.

6. ☒ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☒ For purposes of Appeal, the proposed amendment(s) a)☒ will not be entered or b)☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: _____.

   Claim(s) objected to: _____.

   Claim(s) rejected: *1-8 and 10-19*.

   Claim(s) withdrawn from consideration: *20-22*.

8. ☐ The drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9. ☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10. ☐ Other: _____

ADVISORY ACTION

An appeal under 37 CFR 1.191 was filed in this application on 11-20-2003. Appellant's brief is due on 1-20-2004 in accordance with 37 CFR 1.192(a).

The amendment filed 10-10-2003 under 37 CFR 1.116 in reply to the final rejection has been considered but is not deemed to place the application in condition for allowance and will not be entered because:

The proposed amendment raises new issues that would require further consideration and/or search. Specifically, the proposed amendment to claims 1 and 17 with regard to the periods of stress raise new considerations requiring an additional search.

The declaration by William E. Marshall filed under 37 CFR 1.132 will not be considered because good and sufficient reasons why it was not earlier presented have not been shown. Said declaration addresses issues raised in the Office action mailed 12-17-2002 and should have been submitted in response to said Office.

Since the amendment has not been entered and the declaration has not been considered all rejections are maintained for reasons of record and are reiterated below.

Claim Rejections Maintained

35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 12 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 12 is rendered vague and indefinite by the use of the phrase "stress response factors (SRFs) <10kDa". It is unclear what is meant by said term. If applicant is referring to a molecular weight cutoff the phrase "stress response factors (SRFs) with a molecular weight less than 10kDa" is suggested.

The rejection of claims 17-19 under 35 U.S.C. 112, second paragraph, as being rendered vague and indefinite by the use of the phrase "sequential periods of stress" is maintained for reasons of record.

Applicant argues:

1. The specification clearly states it has "now been found that shorter period of sequential stresses of 20 minutes or less yield more potent SRFs and SRFs of different potencies.
2. The exact length of time is not as important as being one of a series of washings in aqueous buffers of pH 6.0 to 8.0.

Applicant's arguments have been fully considered and deemed non-persuasive. It is still unclear whether the stress factor changes with each successive "period", whether there are rest periods (i.e. removal of stress factors) in between these "periods"? If not, what demarcates the end of one period and the onset of the next? Additionally, claim 18 recites the transferring bacteria to a non-nutritive media and the subsequently transferring the bacteria to non-nutritive media. It is unclear whether this is considered a single "stress period" or multiple periods.

With regard to point 2, it is noted that the features upon which applicant relies (i.e., washings in aqueous buffers of pH 6.0 to 8.0) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The rejection of claims 1-8 and 10-19 under 35 U.S.C. 103(a) as being unpatentable over De Vuyst et al. (Microbiology, Vol. 142, 1996, pages 817-827) is maintained for reasons of record. The cancellation of claim 9 has rendered the rejection of this claim moot.

Applicant argues:

1. Examiner is misinterpreting Applicant's invention that is not related to bacteriocins.

2. The declaration by Dr. Marshall clearly establishes that the SRF compositions of the invention do not include bacteriocins or other compositions with bactericidal properties.

3. The results of Figure 1 demonstrate that the preparations of the invention obtained from *L. monocytogenes, L. plantarum* and *E. faecium* do not inhibit the growth of *Lactobacillus helveticus*.

4. The bacteriocin Nisin does inhibit the growth of *Lactobacillus helveticus*.

5. Figure 2 shows that stressing *L. monocytogenes* or even twice stressing *L. plantarum* and *E. faecium* or stressing heat killed *L. plantarum* and *E. faecium* do not result in bactericidal activity against *L. helveticus*.

6. Figure 3 demonstrates that no bacteriocins against *L. helveticus* are produced by stressing, *L. caseii*, *L. plantarum* or *E. faecium*.

7. Figure 4 shows that the bacteriocin Nisin inhibited 7 strains of bacteria while the SRFs collected from the same strains and *L. caseii* did not inhibit growth.

As outlined previously, De Vuyst et al. disclose methods of producing low molecular weight proteins from bacteria by subjecting them to a number of stresses. By definition, these proteins are stress response factors. These stresses include: a change in temperature, a change in pH, a change in biomass (crowding or decreasing the amount of media), and adding toxins such as ethanol (see abstract). Subjecting the lactic acid bacteria to any of these stressors results in the release of low molecular weight monomers of bacteriocin (approx 6 kDa or less) that oligomerize to be about 30 kDa. De Vuyst et al. remove components larger than the bacteriocin monomer (see page 818, column 1). De Vuyst et al. further disclose that these bacteriocins are able to kill or harm other bacterial species and suggest the use of said bacteriocins as food additives (see page 818, column 1). Consequently, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have followed the suggestion of De Vuyst et al. and administer the low molecular weight proteins produced by stressed bacteria to animals since said proteins (bacteriocins) can act to kill or render harmless other strains of bacteria and thereby enhancing the ability of an animal's immune system to deal with bacterial infections

minimizing the complications associated with introducing a bacterial strain into the normal flora of an animal. Moreover, the internalization of said proteins by an animal would stimulate its the immune system.

Moreover, in response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., the SFR do not have bactericidal properties) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). The instant claims are drawn to **all** factors produced in response to nutrient deprivation.

The rejection of claims 1-8, 10-15 and 17-19 under 35 U.S.C. 103(a) as being unpatentable over De Vuyst et al., cited above, in view of Nanji (U.S. Patent 5,413,785 – IDS-2) is maintained for reasons of record. The cancellation of claim 9 has rendered the rejection of this claim moot.

Applicant argues:

1. There is no suggestion of the claimed invention or the expectation of success in combining the cited references.

2. The cited **reference** does not teach or suggest every element of the claimed invention that must be identically disclosed, in a single reference.

3. It is required that both the suggestion and the expectation of success must be found in prior art. This is not accomplished in regard to De Vuyst et al.

4. SRFs do not directly kill bacteria, as do bacteriocins.

5. Nanji does not reference applicant's SRF that are present in all stressed bacteria.

6. Nanji teaches away from the concept that ordinary lactobacilli that do not inhibit E. coli could, when stressed, provide protection against LPS.

Applicant's arguments have been fully considered and deemed non-persuasive.

With regard to Points 1 and 3, De Vuyst et al. disclose methods for producing low molecular weight proteins from stressed bacteria (bacteriocins) and suggests adding said proteins to food (see above). Nanji discloses the administration of lactic acid bacteria to humans, livestock and other animals for protection against endotoxin-mediated shock. Nanji further discloses that said bacteria should be able to produce anti-microbial substances and/or produce proteinaceous antagonistic substances (bacteriocins) since said substances aid in preventing the growth of gram-positive and gram-negative bacteria in the intestine and thereby reducing endotoxin formation (see column 10, lines 40-45). Reduction of endotoxin levels, in turn, reduces the effects of said endotoxin on the immune processes of the animal. Therefore, it would have been obvious to one of ordinary skill in the art to use the bacteriocins disclosed by De Vuyst et al. in the treatment methodologies of Nanji in order to take advantage of the immune enhancing effects of the bacteriocins while minimizing the complications associated with introducing a bacterial strain into the normal flora of an animal. One would have had a high expectation of success since De Vuyst et al. disclose the use of said bacteriocins as a food additive and Nunji disclose the importance of bacteriocins in reducing endotoxin levels and thereby reducing the deleterious effects of said endotoxin on the animal's immune system.

With regard to Point 2, Applicant is reminded that the rejection was made under 35 U.S.C. 103(a) and not 35 U.S.C. 102. Hence, no single reference needs to disclose all the limitations of the claimed in invention since the rejection is based on the combination of the cited references.

Moreover, in response to applicant's argument that the references fail to show certain features of applicant's invention (Points 4 and 6), it is noted that the features upon which applicant relies (i.e., the SFR do not have bactericidal properties) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). The instant claims are drawn to **all** factors produced in response to nutrient deprivation.

With regard to Point 5, the instant claims are not drawn to SRFs that are produce by all stressed bacteria. The instant claims are drawn to **any** factor (protein) produced in response to nutrient deprivation.

The rejection of claim 16 under 35 U.S.C. 103(a) as being unpatentable over De Vuyst et al., cited above, in view of Perdigon et al. (Journal of Food Protection Vol. 53, No. 5, pages 404-410, 1996 – IDS-2) is maintained for reasons of record.

Applicant argues:

1. Perdigon teaches that the health benefits of feeding milk fermented with lactobacilli is due to the interaction between the bacteria and the milk solids and that these effects are limited to and based upon the presence of milk.

2. Perdigon teaches away from the use of stressed bacteria alone.

Applicant's arguments have been fully considered and deemed non-persuasive.

Claim 16 is being examined as a method of modulating the immune system of an animal by administering low molecular weight stress proteins as an adjuvant.

The teachings of De Vuyst et al. are discussed above. Perdigon et al. disclose the use of lactic acid bacteria and the proteins produced therein as immunogens and adjuvants in the generation of protection from enteropathogens (see abstract, page 404, column 2 and pages 408-409). It would have been obvious to one of ordinary skill in the art at the time the invention was made to **use the low molecular weight proteins disclosed by De Vuyst et al. as adjuvants** for the induction of a immune response to another co-administered pathogen since Perdigon et al. discusses the use of lactic acid bacteria (and the proteins produced by said bacteria) as adjuvants for enteropathogens (an increased immune response to said enteropathogens was also disclosed) and De Vuyst et al. disclose that proteins produced by lactic acid bacteria have an immunomodulatory effect. Consequently, since the lactic acid bacteria serve as the immunogen, they do not need to be separated from the milk in order to meet the limitations of the rejected claim.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert A. Zeman whose telephone number is (703) 308-7991. The examiner can normally be reached on Monday- Thursday, 7am -5:30 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on (703) 308-3909. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

NITA MINNIFIELD
PRIMARY EXAMINER
12/11/03

Robert A. Zeman
December 11, 2003